(FILE 'HOME' ENTERED AT 11:04:48 ON 30 MAR 2001)

FILE 'REGISTRY' ENTERED AT 11:04:57 ON 30 MAR 2001
L1 18 S YLTKEECLKK/SQSP
L2 23 S CTANAVTGPC/SQSP

FILE 'CA' ENTERED AT 11:06:06 ON 30 MAR 2001
L3 7 S L1
L4 8 S L2
L5 1 S L4 NOT L3
L6 0 S MONOKUNIN
L7 1412 S KUNITZ
L8 4 S L3 AND L7
L9 161 S BIKUNIN
L10 27 S L7 AND L9
L11 42 S KUNIN
L12 0 S L11 AND L7
L13 0 S L9 AND L11
L14 287 S URINARY TRYPSIN INHIBITOR OR HEPATOCYTE GROWTH FACTOR ACTIVATOR INHIBITOR
L15 0 S L14 AND L11
L16 32 S L7 AND L14
L17 422 S L9 OR L14 OR L4
L18 154189 S DOMAIN
L19 53 S L17 AND L18

L5 ANSWER 1 OF 1 CA COPYRIGHT 2001 ACS
AN 129:171519 CA
TI Tissue factor pathway inhibitor-3
IN Gentz, Reiner L.; Hsu, Tsu-An; Ni, Jian; Rosen, Craig A.
PA Human Genome Sciences, Inc., USA
SO PCT Int. Appl., 58 pp. CODEN: PIXXD2 DT Patent LA English
FAN.CNT 1
PATENT NO. KIND DATE APPLICATION NO. DATE

PI WO 9833920 A2 19980806 WO 1998-US1468 19980127
WO 9833920 A3 19981105
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG
AU 9860422 A1 19980825 AU 1998-60422 19980127
EP 1005551 A2 20000607 EP 1998-903730 19980127
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
PRAI US 1997-36703 19970131 WO 1998-US1468 19980127
AB The present invention relates to a novel human TFPI-3 protein which is a member of the tissue factor protease inhibitor family. TFPI-3 polypeptides are also provided as are vectors, host cells and recombinant methods for producing the same. The invention further relates to screening methods for identifying agonists and antagonists of TFPI-3 activity. Also provided are diagnostic methods for detecting hemostasis system-related disorders and therapeutic methods for treating hemostatis system-related disorders.

L3 ANSWER 1 OF 7 CA COPYRIGHT 2001 ACS
TI Human cancer-associated gene sequences and polypeptides PY 2000

L3 ANSWER 2 OF 7 CA COPYRIGHT 2001 ACS
TI Kunitz-type serine proteinase inhibitors for accelerating the rate of mucociliary clearance PY 2000

2000

L3 ANSWER 3 OF 7 CA COPYRIGHT 2001 ACS
TI Cloning of a new Kunitz-type protease inhibitor with a putative transmembrane domain overexpressed in pancreatic cancer PY 1998

L3 ANSWER 4 OF 7 CA COPYRIGHT 2001 ACS AN 128:58891 CA
TI Purification and cloning of hepatocyte growth factor activator inhibitor type 2, a Kunitz-type serine protease inhibitor
AU Kawaguchi, Toshiya; Qin, Li; Shimomura, Takeshi; Kondo, Jun; Matsumoto, Kouji; Denda, Kimitoshi; Kitamura, Naomi
CS Research Center, Mitsubishi Chemical Corp., Yokohama, 227, Japan
SO J. Biol. Chem. (1997), 272(44), 27558-27564 CODEN: JBCHA3; ISSN: 0021-9258 PB American Society for Biochemistry and Molecular Biology DT Journal LA English

L3 ANSWER 5 OF 7 CA COPYRIGHT 2001 ACS AN 127:289126 CA
TI Production of functionally active recombinant human bikunin and fragments, blood plasma kallikrein inhibition, and pharmaceutical uses
IN Tamburini, Paul P.; Davis, Gary; Delaria, Katherine A.; Marlor, Christopher W.; Muller, Daniel K.
PA Bayer Corporation, USA; Tamburini, Paul P.; Davis, Gary; Delaria, Katherine A.; Marlor, Christopher W.; Muller, Daniel K.
SO PCT Int. Appl., 110 pp. CODEN: PIXXD2 DT Patent LA English FAN.CNT 1
PATENT NO. KIND DATE APPLICATION NO. DATE

PI WO 9733996 A2 19970918 WO 1997-US3894 19970310
WO 9733996 A3 19971113
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, US, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG
CA 2247888 AA 19970918 CA 1997-2247888 19970310
AU 9722077 A1 19971001 AU 1997-22077 19970310
AU 716923 B2 20000309
EP 891426 A2 19990120 EP 1997-915029 19970310
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
BR 9708021 A 19990727 BR 1997-8021 19970310
CN 1259999 A 20000712 CN 1997-194556 19970310
ZA 9702084 A 19980911 ZA 1997-2084 19970311
PRAI US 1996-13106 19960311 US 1996-19793 19960614 US 1996-725251 19961004 WO 1997-US3894 19970310

L3 ANSWER 6 OF 7 CA COPYRIGHT 2001 ACS
TI Identification and cloning of human placental bikunin, a novel serine protease inhibitor containing two Kunitz dor
PY 1997

L3 ANSWER 7 OF 7 CA COPYRIGHT 2001 ACS AN 126:207827 CA
TI An inhibitor of hepatocyte growth factor activator proteinase activity and a cDNA encoding it and their uses
IN Shimomura, Takeshi; Kawaguchi, Toshiya; Kitamura, Naomi
PA Mitsubishi Chemical Corporation, Japan
SO Eur. Pat. Appl., 24 pp. CODEN: EPXXDW DT Patent LA English FAN.CNT 1
PATENT NO. KIND DATE APPLICATION NO. DATE

PI EP 758682 A2 19970219 EP 1996-111861 19960723
EP 758682 A3 19971112
R: DE, FR, GB
JP 09095498 A2 19970408 JP 1996-193584 19960723
US 5731412 A 19980324 US 1996-685660 19960724
US 5854396 A 19981229 US 1997-974196 19971119
PRAI JP 1995-187134 19950724 US 1996-685660 19960724

L8 ANSWER 1 OF 4 CA COPYRIGHT 2001 ACS

TI *Kunitz*-type serine proteinase inhibitors for accelerating the rate of mucociliary clearance

L8 ANSWER 2 OF 4 CA COPYRIGHT 2001 ACS
TI Cloning of a new *Kunitz*-type protease inhibitor with a putative transmembrane domain overexpressed in pancreatic cancer

L8 ANSWER 3 OF 4 CA COPYRIGHT 2001 ACS
TI Purification and cloning of hepatocyte growth factor activator inhibitor type 2, a *Kunitz*-type serine protease inhibitor

L8 ANSWER 4 OF 4 CA COPYRIGHT 2001 ACS
TI Identification and cloning of human placental bikunin, a novel serine protease inhibitor containing two*Kunitz*domains

L10 ANSWER 1 OF 27 CA COPYRIGHT 2001 ACS
TI Hepatocyte growth factor activator inhibitor type 1 is a specific cell surface binding protein of hepatocyte growth factor activator (HGFA) and regulates HGFA activity in the pericellular microenvironmentPY 2000

L10 ANSWER 2 OF 27 CA COPYRIGHT 2001 ACS
TI α1-Microglobulin: a yellow-brown lipocalin PY 2000

L10 ANSWER 3 OF 27 CA COPYRIGHT 2001 ACS
TI Suppression of urokinase-type plasminogen activator expression from human ovarian cancer cells by urinary trypsin inhibitor PY 2000

L10 ANSWER 4 OF 27 CA COPYRIGHT 2001 ACS
TI Genomic structure and chromosomal localization of the human hepatocyte growth factor activator inhibitor type 1 and 2 genes PY 2000

L10 ANSWER 5 OF 27 CA COPYRIGHT 2001 ACS AN 133:84295 CA
TI *Kunitz*-type serine proteinase inhibitors for accelerating the rate of mucociliary clearance
IN Hall, Roderick; Poll, Christopher T.; Newton, Benjamin B.; Taylor, William J. A.
PA Bayer Aktiengesellschaft, Germany
SO PCT Int. Appl., 173 pp. CODEN: PIXXD2 DT Patent LA English FAN.CNT 1
PATENT NO. KIND DATE APPLICATION NO. DATE

PI WO 2000037099 A2 20000629 WO 1999-GB4381 19991222
WO 2000037099 A3 20001026
W: AE, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, CZ, DE, DE, DK, DK, DM, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRAI US 1998-218913 19981222 US 1999-441966 19991117

L10 ANSWER 6 OF 27 CA COPYRIGHT 2001 ACS
TI Proteoglycan core protein in human urine and its possible role on calcium oxalate urolithiasisPY 1999

L10 ANSWER 7 OF 27 CA COPYRIGHT 2001 ACS
TI Generation of catalytically active granzyme K from Escherichia coli inclusion bodies and identification of efficient granzyme K inhibitors in human plasma PY 1999

L10 ANSWER 8 OF 27 CA COPYRIGHT 2001 ACS
TI Urinary trypsin inhibitor down-regulates hyaluronic acid fragment-induced prostanoid release in cultured human amnion cells by inhibiting cyclo-oxygenase-2 expression PY 1999

L10 ANSWER 9 OF 27 CA COPYRIGHT 2001 ACS
TI Detection of *bikunin* mRNA in limited portions of rat brain PY 1999

L10 ANSWER 10 OF 27 CA COPYRIGHT 2001 ACS
TI Temporal changes in mRNA expression for *bikunin* in the kidneys of rats during calcium oxalate nephrolithiasis PY 1999

L10 ANSWER 11 OF 27 CA COPYRIGHT 2001 ACS
TI Guinea pig α1-microglobulin/ *bikunin*: cDNA sequencing, tissue expression and expression during acute phase PY 1999

L10 ANSWER 12 OF 27 CA COPYRIGHT 2001 ACS AN 130:207692 CA
TI Assembly and secretion of recombinant chains of human inter-α- trypsin inhibitor in COS-7 cells
AU Martin-Vandelet, Nathalie; Paris, Sebastien; Bourguignon, Jeannette; Sesboue, Richard; Martin, Jean-Pierre; Diarra-Mehrpour, Maryam
CS Laboratoire de Physiopathologie et Genetique Renale et Pulmonaire, Institut National de la Sante et de la Recherche Medicale, INSERM Unite 295, Faculte de Medecine de Rouen, and IFR 61: phy, Rouen, F-76183, Fr.
SO Eur. J. Biochem. (1999), 259(1/2), 476-484 CODEN: EJBCAI; ISSN: 0014-2956 PB Blackwell Science Ltd. DT Journal LA English
AB The inter-α-trypsin inhibitor (ITI) family is a group of structurally related plasma serine protease inhibitors. The ITI family members consist of combinations of mature heavy chains named HC1, HC2, HC3 linked to *bikunin* (a *Kunitz*-type protease inhibitor) by a covalent interchain protein-glycosaminoglycan-protein cross-link. The biosynthesis of the ITI family members takes place in the liver. In this report we examine the biosynthesis of these proteins using transient transfected COS-7 cells expressing one or more combinations of human ITI chains. The processing and secretion of α1-microglobulin and *bikunin* does not require the ITI heavy chains. A small proportion of the H3 chain seems to be processed into the HC3 form in the absence of the other ITI chains. In contrast, the processing of H2 into HC2 needs the presence of the L chain. The COS-7 cells are able to link the HC2 and HC3 heavy chains with *bikunin* by means of a chondroitin sulfate bridge, and thus to generate 260-kDa ITI-like proteins as well as pre-α-trypsin inhibitor (Pαl). However, the maturation of the H1 chain into HC1 and the assembly of HC1 inside multichain proteins may take place according to a mechanism which differs from that of the H2 and H3 chains. These results indicate that the assembly of the constituent chains of the ITI-like proteins and Pαl is not dependent on the liver machinery.
RE.CNT 31 RE
(1) Balduyck, M; Biol Chem Hoppe Seyler 1989, V370, P329 CA
(2) Blom, A; Biochem J 1997, V328, P185 CA
(3) Bost, F; Eur J Biochem 1998, V252, P339 CA
(4) Bourguignon, J; Biochem J 1989, V261, P305 CA
(5) Bourguignon, J; Eur J Biochem 1993, V212, P771 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 13 OF 27 CA COPYRIGHT 2001 ACS AN 129:2052 CA
TI The crystal structure of *Bikunin* from the inter-α- inhibitor complex: a serine protease inhibitor with two *Kunitz* domains
AU Xu, Yibin; Carr, Paul D.; Guss, J. Mitchell; Ollis, David L.
CS Research School of Chemistry, Australian National University, Canberra, ACT 2601, Australia
SO J. Mol. Biol. (1998), 276(5), 955-966 CODEN: JMOBAK; ISSN: 0022-2836 PB Academic Press Ltd. DT Journal LA English
AB *Bikunin* is a serine protease inhibitor found in the blood serum and urine of humans and other animals. Its sequence shows internal repetition, suggesting that it contains two domains that resemble bovine pancreatic trypsin inhibitor (BPTI). A fragment of *bikunin* has been crystd., its structure solved and subsequently refined against 2.5 .ANG. data. The two BPTI-like domains pack closely together and are related by an approx. 60.degree. rotation combined with a translation. These domains are very similar to each other and other proteins with this fold. The largest variations occur in the loops responsible for protease recognition. The loops of the first domain are unobstructed by the remaining protein. However, the loops of the second domain are close to the first domain and it is possible that protease binding m[illegible] be affected or, in some cases, abolished by the presence of the first domain. Thus, cleavage of the tw[illegible] domains could alter the substrate pecificity of domain II. *Bikunin* has a hydrophobic patch close to the N terminus of domain I, which is the most likely site for cell-surface receptor binding. In addn., there is a basic patch at one end of domain II that may be responsible for the inhibition of calcium oxalate crystn. in urine.

L10 ANSWER 14 OF 27 CA COPYRIGHT 2001 ACS
TI Inhibition of tryptase TL2 from human T4+ lymphocytes and inhibition of HIV-1 replication in H9 cells by recombinant aprotinin and *bikunin* homologs PY 1997

L10 ANSWER 15 OF 27 CA COPYRIGHT 2001 ACS
TI Recombinant preparation in Pichia of human protease inhibitor mutants with improved activity on inhibiting neutrophil elastase PY 1997

L10 ANSWER 16 OF 27 CA COPYRIGHT 2001 ACS
TI Identification and cloning of human placental *bikunin*, a novel serine protease inhibitor containing two *Kunitz*domains PY 1997

L10 ANSWER 17 OF 27 CA COPYRIGHT 2001 ACS
TI Characterization of placental *bikunin*, a novel human serine protease inhibitor PY 1997

L10 ANSWER 18 OF 27 CA COPYRIGHT 2001 ACS
TI Strong crossreaction of human anti-aprotinin antibodies from heart transplant patient with [Arg15]aprotinin PY 1997

L10 ANSWER 19 OF 27 CA COPYRIGHT 2001 ACS
TI Human urinary trypsin inhibitor and fragments and their recombinant preparation with Pichia PY 1996

L10 ANSWER 20 OF 27 CA COPYRIGHT 2001 ACS
TI Sequence analysis and evolutionary aspects of piscine α-1- microglobulin/ *bikunin* mRNA transcripts PY 1995

L10 ANSWER 21 OF 27 CA COPYRIGHT 2001 ACS
TI Isolation and characterization of novel blood coagulation factor Xa (FXa) inhibitor (R-020) and its variants PY 1994

L10 ANSWER 22 OF 27 CA COPYRIGHT 2001 ACS
TI Sequencing of cDNAs encoding α1-microglobulin/ *bikunin* of Mongolian gerbil and Syrian golden hamster in omparison with man and other species PY 1994

L10 ANSWER 23 OF 27 CA COPYRIGHT 2001 ACS
TI Developmentally regulated transcription of the four liver-specific genes for inter-α-inhibitor family in mouse PY 1993

L10 ANSWER 24 OF 27 CA COPYRIGHT 2001 ACS
TI Mouse α-1-microglobulin/ *bikunin* precursor: cDNA analysis, gene evolution and physical assignment of the gene next to the orosomucoid locus PY 1993

L10 ANSWER 25 OF 27 CA COPYRIGHT 2001 ACS
TI Homologous chromosomal locations of the four genes for inter-α-inhibitor and pre-α-inhibitor family in human and mouse: assignment of the ancestral gene for the lipocalin superfamily PY 1992

L10 ANSWER 26 OF 27 CA COPYRIGHT 2001 ACS AN 115:107384 CA
TI Structure of the human α1-microglobulin- *bikunin* gene
AU Vetr, Helga; Gebhard, Wolfgang
CS Klin. Grosshadern, Ludwig-Maximilians-Univ., Munich, W-8000/70, Fed. Rep. Ger.
SO Biol. Chem. Hoppe-Seyler (1990), 371(12), 1185-96 CODEN: BCHSEI; ISSN: 0177-3593 DT Journal LA English
AB α1-Microglobulin (protein HC) and *bikunin* (formerly HI-30, urinary trypsin inhibitor, inhibitor subunit of inter-α-(trypsin) inhibitor) are abundant serum glycoproteins. They belong to 2 distinct protein families, the lipocalin family, a family of transport proteins for small hydrophobic mols. and the *Kunitz*-family of proteinase inhibitors. Mature α1-microglobulin and *bikunin* result from a common precursor. The human gene coding for this precursor protein was isolated and sequenced. The gene consists of 10 exons which span 1.3 kb and 9 introns with an aggregate length of about 16.5 kb. The largest intron (6.5 kb) separates exon 6 (coding for the C-terminal sequence of α1-microglobulin) from exon 7 (coding for a linker peptide and the N-terminal peptide of *bikunin*). Repetitive DNA sequences of the Alu-type occur downstream of the polyadenylation site, within introns 4 and 6, and upstream of the putative promoter region which has been defined by sequence comparison and transcription start site detn. The gene also contains several sequence motifs reminiscent to known enhancer sequences.

L10 ANSWER 27 OF 27 CA COPYRIGHT 2001 ACS
TI Structure of inter-α-inhibitor (inter-α-trypsin inhibitor) and pre-α-inhibitor: current state and proposition of a new terminologyPY 1990

L16 ANSWER 1 OF 32 CA COPYRIGHT 2001 ACS
TI *Hepatocyte**growth**factor**activator**inhibitor* type 1 is a specific cell surface binding protein of hepatocyte growth factor activator (HGFA) and regulates HGFA activity in the pericellular microenvironment PY 2000

L16 ANSWER 2 OF 32 CA COPYRIGHT 2001 ACS
TI Localization of *hepatocyte**growth**factor**activator**inhibitor* type 1 in Langhans' cells of human placenta PY 2000

L16 ANSWER 3 OF 32 CA COPYRIGHT 2001 ACS
TI Suppression of urokinase-type plasminogen activator expression from human ovarian cancer cells by *urinary**trypsin**inhibitor*PY 2000

L16 ANSWER 4 OF 32 CA COPYRIGHT 2001 ACS
TI Identification and characterization of a *Kunitz*-type protease inhibitor in ascites fluid from patients with ovarian carcinoma PY 2000

L16 ANSWER 5 OF 32 CA COPYRIGHT 2001 ACS
TI Genomic structure and chromosomal localization of the human *hepatocyte**growth**factor**activator**inhibitor* type 1 and 2 genes PY 2000

L16 ANSWER 6 OF 32 CA COPYRIGHT 2001 ACS
TI Identity of *urinary**trypsin**inhibitor* -binding protein to link protein PY 2000

L16 ANSWER 7 OF 32 CA COPYRIGHT 2001 ACS
TI Upregulation of HGF activator inhibitor type 1 but not type 2 along with regeneration of intestinal mucosa PY 2000

L16 ANSWER 8 OF 32 CA COPYRIGHT 2001 ACS
TI Multiple sites of proteolytic cleavage to release soluble forms of *hepatocyte**growth**factor**activator**inhibitor* type 1 from a transmembrane form PY 1999

L16 ANSWER 9 OF 32 CA COPYRIGHT 2001 ACS
TI *Urinary**trypsin**inhibitor* down-regulates hyaluronic acid fragment-induced prostanoid release in cultured human amnion cells by inhibiting cyclo-oxygenase-2 expression PY 1999

L16 ANSWER 10 OF 32 CA COPYRIGHT 2001 ACS AN 130:334283 CA
TI *Hepatocyte**Growth**Factor**Activator**Inhibitor* Type 2 Lacking the First *Kunitz*-Type Serine Proteinase Inhibitor Domain Is a Predominant Product in Mouse but Not in Human
AU Itoh, Hiroshi; Kataoka, Hiroaki; Hamasuna, Ryoichi; Kitamura, Naomi; Koono, Masashi
CS Second Department of Pathology, Miyazaki Medical College, Kiyotake, Miyazaki, 889-1692, Japan
SO Biochem. Biophys. Res. Commun. (1999), 255(3), 740-748 CODEN: BBRCA9; ISSN: 0006-291X PB Academic Press DT Journal LA English
AB *Hepatocyte**growth**factor**activator**inhibitor* type 2 (HAI-2) is a new *Kunitz*-type serine protease inhibitor, which is purified and cloned from human stomach cancer cell line MKN45. The mature HAI-2 protein contains two *Kunitz* domains and the first domain is mainly responsible for the inhibitory activity against hepatocyte growth factor activator (HGFA). In this study, we identified the mouse homolog of HAI-2 (mHAI-2) by screening the data base of public expressed sequence tag (dbEST). In addn. to a full-length cDNA corresponding to human HAI-2, a shorter size of mHAI-2 cDNA was obtained from mouse kidney by reverse-transcription polymerase chain reaction (RT-PCR). Sequence anal. of this shorter cDNA revealed that the region encoding the first *Kunitz* domain was completely deleted. Anal. of mouse genomic DNA showed that the deleted cDNA was generated by an alternative splicing mechanism. Surprisingly, the spliced form lacking the first *Kunitz* domain was a predominant transcript in all tissues of mice tested but not in those of human as assessed by RT-PCR anal. This phenomenon is also confirmed by Western blot anal. using the specific antiserum against human HAI-2 protein. These results suggest that most of HAI-2 expressed in various tissues of mice may be unable to inhibit HGFA efficiently. (c) 1999 Academic Press.
RE.CNT 34 RE
(1) Chang, J; Thromb Haemost 1998, V79, P306 CA
(2) Chu, M; EMBO J 1990, V9, P385 CA
(3) Delaria, K; J Biol Chem 1997, V272, P12209 CA
(4) Diarra-Mehrpour, M; Eur J Biochem 1990, V191, P131 CA
(5) Gebhard, W; Proteinase Inhibitors 1986, P375 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 11 OF 32 CA COPYRIGHT 2001 ACS
TI White matter astrocytes produce *hepatocyte**growth**factor**activator**inhibitor* in human brain tissues PY 1999

L16 ANSWER 12 OF 32 CA COPYRIGHT 2001 ACS AN 130:11863 CA
TI Functional characterization of *Kunitz* domains in *hepatocyte**growth**factor**activator**inhibitor* type 2
AU Qin, Li; Denda, Kimitoshi; Shimomura, Takeshi; Kawaguchi, Toshiya; Kitamura, Naomi
CS Faculty of Bioscience and Biotechnology, Department of Life Science, Tokyo Institute of Technology, Yokohama, 226, Japan
SO FEBS Lett. (1998), 436(1), 111-114 CODEN: FEBLAL; ISSN: 0014-5793 PB Elsevier Science B.V.
DT Journal LA English
AB *Hepatocyte**growth**factor**activator**inhibitor* type 2 (HAI-2) was identified as a potent inhibitor of hepatocyte growth factor activator (HGF activator). The primary translation product of HAI-2 contains two *Kunitz* domains. To characterize their function, we introduced a point mutation into the reactive site of each *Kunitz* domain, and assayed the mutants for their HGF activator inhibitory activity. A point mutation in the COOH-terminal *Kunitz* domain did not affect the activity of HAI-2, whereas a point mutation in the NH2-terminal *Kunitz* domain markedly reduced the activity. These results suggest that the NH2-terminal *Kunitz* domain is mainly responsible for the HGF activator inhibitory activity of HAI-2.
RE.CNT 21 RE
(1) Delaria, K; J Biol Chem 1997, V272, P12209 CA
(2) Derijard, B; Cell 1994, V76, P1025 CA

(3) Girard, T; Nature 1989, V338, P518 CA
(4) Gohda, E; J Clin Invest 1988, V81, P414 CA
(5) Igawa, T; Biochem Biophys Res Commun 1991, V174, P831 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 13 OF 32 CA COPYRIGHT 2001 ACS
TI *Urinary**trypsin**inhibitor* reduces the release of histamine from rat peritoneal mast cells PY 1998

L16 ANSWER 14 OF 32 CA COPYRIGHT 2001 ACS
TI Evaluation of *hepatocyte**growth**factor**activator**inhibitor* expression in normal and malignant colonic mucosa PY 1998

L16 ANSWER 15 OF 32 CA COPYRIGHT 2001 ACS
TI Role of O-linked carbohydrate of human *urinary**trypsin**inhibitor* on its lysosomal membrane-stabilizing property PY 1998

L16 ANSWER 16 OF 32 CA COPYRIGHT 2001 ACS
TI *Urinary**trypsin**inhibitor*, a *Kunitz* -type protease inhibitor, modulates tumor necrosis factor-stimulated activation and translocation of protein kinase C in U937 cells PY 1998

L16 ANSWER 17 OF 32 CA COPYRIGHT 2001 ACS
TI Purification and cloning of *hepatocyte**growth**factor**activator**inhibitor* type 2, a *Kunitz*-type serine protease inhibitor PY 1997

L16 ANSWER 18 OF 32 CA COPYRIGHT 2001 ACS AN 127:216908 CA
TI Purification and characterization of a novel protease inhibitor specific to hepatocyte growth factor activator
AU Kawaguchi, Toshiya; Shimomura, Takeshi; Denda, Kimitoshi; Kitamura, Akiko; Kondo, Jun; Kito, Masahiro; Kagaya, Shinji; Qin, Li; Takata, Hiroyuki; Miyazawa, Keiji; Kitamura, Naomi
CS Yokohama Research Center, Mitsubishi Chemical Corporation, Yokohama, 227, Japan
SO Anim. Cell Technol.: Basic Appl. Aspects, Proc. Annu. Meet. Jpn. Assoc. Anim. Cell Technol., 8th (1997), Meeting Date 1995, 403-407. Editor(s): Funatsu, Kazumori; Shirai, Yoshihito; Matsushita, Taku. Publisher: Kluwer, Dordrecht, Neth. CODEN: 64WUA2 DT Conference LA English
AB *Hepatocyte**growth**factor**activator**inhibitor* (HAI) was purified from serum-free conditioned medium of a human stomach carcinoma cell line, and a partial amino acid sequence was detd. The sequence data revealed that HAI is a novel proteinase inhibitor which contains a *Kunitz*-type serine proteinase inhibitory domain. Purified HAI inhibited hepatocyte growth factor activator in a concn.-dependent manner, but had no significant effect on factor XIIa.

L16 ANSWER 19 OF 32 CA COPYRIGHT 2001 ACS
TI Novel protease inhibitory activities of the second domain of urinary trypsin inhibitory (R-020) and its effect on sepsis-induced organ injury in rat PY 1996

L16 ANSWER 20 OF 32 CA COPYRIGHT 2001 ACS
TI Recombinant preparation in Pichia of human protease inhibitor mutants with improved activity on inhibiting neutrophil elastase PY 1997

L16 ANSWER 21 OF 32 CA COPYRIGHT 2001 ACS
TI *Hepatocyte**growth**factor**activator**inhibitor*, a novel *Kunitz*-type serine protease inhibitor PY 1997

L16 ANSWER 22 OF 32 CA COPYRIGHT 2001 ACS AN 124:336669 CA
TI Human *urinary**trypsin**inhibitor* and fragments and their recombinant preparation with Pichia
IN Ideno, Shoji; Goto, Takashi; Horii, Hajime
PA Green Cross Corporation, Japan
SO PCT Int. Appl., 97 pp. CODEN: PIXXD2 DT Patent LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9603503	A1	19960208	WO 1995-JP1449	19950721

W: CA, CN, JP, KR, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
PRAI JP 1994-169221 19940721
AB A process for producing a urinary human trypsin inhibitor (UTI) and domains thereof by using a yeast of the genus Pichia is described. The method involves the construction of expression plasmid contg. AOX1 promoter and SUC2. Plasmid pHH313 encoding *Kunitz* type domain I with addnl. 21 amino acids at its N-terminus and plasmid pHH314 encoding *Kunitz* type domain II were prepd. and used for the transformation of Pichia strain GTS115. *Kunitz* type domain II purified from the culture supernatant exhibited significant trypsin-inhibitory activity, but little inhibition to human neutrophil elastase. Ep1-UTI, a UTI mutant having the active site MGMTS replaced with IAFFP, was also prepd. and its improved elastase-inhibitory activity demonstrated. Prepn. and characterization of mutant Ep1-d21 having its N-terminal 21 amino acids deleted were also shown. The methods of this invention can be optimized for mass prodn. of UTI for use as therapeutics.

L16 ANSWER 23 OF 32 CA COPYRIGHT 2001 ACS
TI *Kunitz*-type trypsin inhibitor prevents LPS-induced increase of cytosolic free Ca2+ in human neutrophils and HUVEC cells PY 1995

L16 ANSWER 24 OF 32 CA COPYRIGHT 2001 ACS
TI Isolation and characterization of novel blood coagulation factor Xa (FXa) inhibitor (R-020) and its variants PY 1994

L16 ANSWER 25 OF 32 CA COPYRIGHT 2001 ACS
TI Down-regulation of interleukin-8 gene expression in HL60 cell line by human *Kunitz*-type trypsin inhibitor PY 1995

L16 ANSWER 26 OF 32 CA COPYRIGHT 2001 ACS
TI Protective effect of recombinant neutrophil elastase inhibitor (R-020) on sepsis-induced organ injury in rat PY 1994

L16 ANSWER 27 OF 32 CA COPYRIGHT 2001 ACS AN 120:211333 CA
TI Novel factor Xa and plasma kallikrein inhibitory activities of the second *Kunitz*-type inhibitory domain of *urinary**trypsin**inhibitor*
AU Morishita, Hideaki; Yamakawa, Toru; Matsusue, Tomokazu; Kusuyama, Takeshi; Sameshima-Aruga, Rie; Hirose, Jiro; Nii, Atsushi; Miura, Toshihisa; Isaji, Mitsuko; et al.
CS Biosci. Res. Lab., Mochida Pharm. Co. Ltd., Tokyo, 115, Japan
SO Thromb. Res. (1994), 73(3-4), 193-204 CODEN: THBRAA; ISSN: 0049-3848 DT Journal LA English
AB *Urinary**trypsin**inhibitor* is a glycoprotein with a structure in which 2 *Kunitz*-type inhibitory domains are linked in a row. Two genes were isolated encoding the 70-amino-acid sequence from the 78th amino acid (Thr) to the C-terminal and the 68-amino-acid sequence from the 80th (Ala) to C-terminal of human *urinary**trypsin**inhibitor*, both which correspond to the 2nd *Kunitz*-type inhibitory domain, and then expression plasmids were constructed by ligating it to the Echerichia coli alk. phosphatase signal peptide gene. These plasmids under the control of the tryptophan promoter expressed the 2nd domain in E. coli strain JE5505 which lacks the membrane lipoprotein. The recombinant 2nd domain purified from the culture supernatant of the transformant inhibited trypsin, plasmin, leukocyte elastase, and chymotrypsin which are known to be inhibited by *urinary**trypsin**inhibitor*. In addn. it inhibited blood coagulation factor Xa and plasma kallikrein in a concn.-dependent and competitive manner, and significantly prolonged the plasma-based activated partial thromboplastin time (APTT). The truncated natural counterpart obtained by a limited degrdn. of human *urinary**trypsin**inhibitor* revealed identical inhibitory activities.

L16 ANSWER 28 OF 32 CA COPYRIGHT 2001 ACS
TI Structure of the human α1-microglobulin-bikunin gene PY 1990

L16 ANSWER 29 OF 32 CA COPYRIGHT 2001 ACS
TI Structure of inter-α-inhibitor (inter-α-trypsin inhibitor) and pre-α-inhibitor: current state and proposition of a new terminology PY 1990

L16 ANSWER 30 OF 32 CA COPYRIGHT 2001 ACS
TI cDNA cloning of human inter-α-trypsin inhibitor discloses three different proteins PY 1987

L16 ANSWER 31 OF 32 CA COPYRIGHT 2001 ACS AN 96:48145 CA
TI *Kunitz*-type proteinase inhibitors derived by limited proteolysis of the inter-α-trypsin inhibitor. V. Attachments of carbohydrates in the human *urinary*trypsin*inhibitor* isolated by affinity chromatography
AU Hochstrasser, Karl; Schoenberger, Oeyvind L.; Rossmanith, Ingrid; Wachter, Elmar
CS Biochem. Labor Klin., Univ. Muenchen, Munich, Fed. Rep. Ger.
SO Hoppe-Seyler's Z. Physiol. Chem. (1981), 362(10), 1357-62 CODEN: HSZPAZ; ISSN: 0018-4888 DT Journal LA English
AB Trypsin inhibitor HI-30 of human urine, physiol. released from inter-α-trypsin inhibitor and having a known peptide sequence, was purified by affinity chromatog. and its carbohydrate structure was detd. The carbohydrates, which comprise .apprx.50 of the inhibitor, are attached to the peptide moiety at 2 sites. One chain is linked O-glycosidically via serine-10 in the N-terminal extension peptide and the other is linked N-glucosidically via arginine-24 in the inactive inhibitory *Kunitz* -type domain of the inhibitor. The complete sequences of the carbohydrate chains were detd.

L16 ANSWER 32 OF 32 CA COPYRIGHT 2001 ACS AN 96:48144 CA
TI *Kunitz*-type proteinase inhibitors derived by limited proteolysis of the inter-α-trypsin inhibitor. IV. The amino acid sequence of the human *urinary**trypsin**inhibitor* isolated by affinity chromatography
AU Wachter, Elmar; Hochstrasser, Karl
CS Inst. Physiol. Chem. Phys. Biochem. Zellbiol., Univ. Muenchen, Munich, Fed. Rep. Ger.
SO Hoppe-Seyler's Z. Physiol. Chem. (1981), 362(10), 1351-5 CODEN: HSZPAZ; ISSN: 0018-4888 DT Journal LA English
AB The amino acid sequence of the complete polypeptide chain of human *urinary**trypsin**inhibitor* HI-30, physiol. released from human inter-α-trypsin inhibitor and comprised of a C-terminal domain with antitrypsin activity and a domain displaying no inhibitory activity, was detd. Both the N-terminal extension peptide with 21 residues and the inactive domain are linked O- and N-glycosidically, resp., to large carbohydrate moieties. The N-terminal amino acid sequence of the inhibitor was detd. by solid-phase Edman degrdn. of a single peptide. The mol. wt. calcd. for the total polypeptide chain of 143 residues was 15,340. In consideration of the difference between this value and the exptl. detd. value (30,000), the glycopeptide evidently contains a carbohydrate moiety of considerable mol. wt.

L19 ANSWER 1 OF 53 CA COPYRIGHT 2001 ACS
TI *Hepatocyte**growth**factor**activator**inhibitor* type 1 is a specific cell surface binding protein of hepatocyte growth factor activator (HGFA) and regulates HGFA activity in the pericellular microenvironment PY 2000

L19 ANSWER 2 OF 53 CA COPYRIGHT 2001 ACS
TI Method for identifying toxic agents in liver tissues using differential gene expression PY 2001

L19 ANSWER 3 OF 53 CA COPYRIGHT 2001 ACS
TI Identification and characterization of a Kunitz-type protease inhibitor in ascites fluid from patients with ovarian carcinoma PY 2000

L19 ANSWER 4 OF 53 CA COPYRIGHT 2001 ACS
TI Genomic structure and chromosomal localization of the human *hepatocyte**growth**factor**activator**inhibitor* type 1 and 2 genes PY 2000

L19 ANSWER 5 OF 53 CA COPYRIGHT 2001 ACS
TI Identity of *urinary**trypsin**inhibitor* -binding protein to link protein PY 2000

L19 ANSWER 6 OF 53 CA COPYRIGHT 2001 ACS
TI Upregulation of HGF activator inhibitor type 1 but not type 2 along with regeneration of intestinal mucosa PY 2000

L19 ANSWER 7 OF 53 CA COPYRIGHT 2001 ACS
TI Proteoglycan core protein in human urine and its possible role on calcium oxalate urolithiasis PY 1999

L19 ANSWER 8 OF 53 CA COPYRIGHT 2001 ACS
TI Multiple sites of proteolytic cleavage to release soluble forms of *hepatocyte**growth**factor**activator**inhibitor* type 1 from a transmembrane form PY 1999

L19 ANSWER 9 OF 53 CA COPYRIGHT 2001 ACS
TI Generation of catalytically active granzyme K from Escherichia coli inclusion bodies and identification of efficient granzyme K inhibitors in human plasma PY 1999

L19 ANSWER 10 OF 53 CA COPYRIGHT 2001 ACS
TI Expression vectors for eukaryotic cells that direct accurate splicing of primary transcripts PY 1999 1999 2000

L19 ANSWER 11 OF 53 CA COPYRIGHT 2001 ACS
TI Guinea pig α1-microglobulin/ *bikunin*: cDNA sequencing, tissue expression and expression during acute phase PY 1999

L19 ANSWER 12 OF 53 CA COPYRIGHT 2001 ACS
TI *Hepatocyte**Growth**Factor**Activator**Inhibitor* Type 2 Lacking the First Kunitz-Type Serine Proteinase Inhibitor *Domain* Is a Predominant Product in Mouse but Not in Human PY 1999

L19 ANSWER 13 OF 53 CA COPYRIGHT 2001 ACS
TI Structural characterization of inter-α-inhibitor. Evidence for an extended shape PY 1999

L19 ANSWER 14 OF 53 CA COPYRIGHT 2001 ACS
TI Fusion proteins of receptor ligand-binding domains and proteinase inhibitors for inhibition of cell migration PY 1998 1999 1998 2000 2000

L19 ANSWER 15 OF 53 CA COPYRIGHT 2001 ACS AN 130:11863 CA
TI Functional characterization of Kunitz domains in *hepatocyte**growth**factor**activator**inhibitor* type 2
AU Qin, Li; Denda, Kimitoshi; Shimomura, Takeshi; Kawaguchi, Toshiya; Kitamura, Naomi
CS Faculty of Bioscience and Biotechnology, Department of Life Science, Tokyo Institute of Technology, Yokohama, 226, Japan
SO FEBS Lett. (1998), 436(1), 111-114 CODEN: FEBLAL; ISSN: 0014-5793PB Elsevier Science B.V.
DT Journal LA English
AB *Hepatocyte**growth**factor**activator**inhibitor* type 2 (HAI-2) was identified as a potent inhibitor of hepatocyte growth factor activator (HGF activator). The primary translation product of HAI-2 contains two Kunitz domains. To characterize their function, we introduced a point mutation into the reactive site of each Kunitz *domain*, and assayed the mutants for their HGF activator inhibitory activity. A point mutation in the COOH-terminal Kunitz *domain* did not affect the activity of HAI-2, whereas a point mutation in the NH2-terminal Kunitz *domain* markedly reduced the activity. These results suggest that the NH2-terminal Kunitz *domain* is mainly responsible for the HGF activator inhibitory activity of HAI-2.
RE.CNT 21 RE
(1) Delaria, K; J Biol Chem 1997, V272, P12209 CA
(2) Derijard, B; Cell 1994, V76, P1025 CA
(3) Girard, T; Nature 1989, V338, P518 CA
(4) Gohda, E; J Clin Invest 1988, V81, P414 CA
(5) Igawa, T; Biochem Biophys Res Commun 1991, V174, P831 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 16 OF 53 CA COPYRIGHT 2001 ACS AN 129:171519 CA
TI Tissue factor pathway inhibitor-3
IN Gentz, Reiner L.; Hsu, Tsu-An; Ni, Jian; Rosen, Craig A.
PA Human Genome Sciences, Inc., USA
SO PCT Int. Appl., 58 pp. CODEN: PIXXD2 DT Patent LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9833920	A2	19980806	WO 1998-US1468	19980127
WO 9833920	A3	19981105		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG
AU 9860422 A1 19980825 AU 1998-60422 19980127
EP 1005551 A2 20000607 EP 1998-903730 19980127
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
PRAI US 1997-36703 19970131 WO 1998-US1468 19980127
AB The present invention relates to a novel human TFPI-3 protein which is a member of the tissue factor protease inhibitor family. TFPI-3 polypeptides are also provided as are vectors, host cells and recombinant methods for producing the same. The invention further relates to screening methods for identifying agonists and antagonists of TFPI-3 activity. Also provided are diagnostic methods for detecting hemostasis system-related disorders and therapeutic methods for treating hemostatis system-related disorders.

L19 ANSWER 17 OF 53 CA COPYRIGHT 2001 ACS
TI A bifunctional hybrid molecule of the amino-terminal fragment of urokinase and *domain* II of *bikunin* efficiently inhibits tumor cell invasion and metastasis PY 1998

L19 ANSWER 18 OF 53 CA COPYRIGHT 2001 ACS AN 129:144599 CA
TI A bifunctional hybrid molecule of urokinase amino-terminal fragment and *bikunin**domain* II efficiently inhibits tumor cell invasion and metastasis
AU Kobayashi, H.; Terao, T.
CS Department of Obstetrics and Gynecology, Hamamatsu University School of Medicine, Shizuoka, 431-31, Japan
SO Int. Congr. Ser. (1997), 1129(Recent Progress in Blood Coagulation and Fibrinolysis), 249-252 CODEN: EXMDA4; ISSN: 0531-5131 PB Elsevier Science B.V. DT Journal LA English
AB *Urinary**trypsin**inhibitor* (UTI) efficiently inhibits tumor cell invasion and the formation of metastasis. The anti-metastatic effect is dependent on the COOH-terminal *domain*II of UTI (HI-8). In order to develop a mol. that binds with high affinity to the urokinase receptor (uPAR) on tumor cell

surface, a bifunctional hybrid mol. (ATFHI) consisting of the uPAR-binding amino-terminal fragment (ATF) of uPA (amino acid sequence 1-134) at the NH2-terminus of HI-8 was produced in Escherichia coli by protein engineering.

L19 ANSWER 19 OF 53 CA COPYRIGHT 2001 ACS
TI Identification of structural domains in inter-α-trypsin inhibitor involved in calcium oxalate crystallization PY 1998

L19 ANSWER 20 OF 53 CA COPYRIGHT 2001 ACS
TI Preparation and use of drugs containing phospholipid-targeting peptides PY 1998 1999

L19 ANSWER 21 OF 53 CA COPYRIGHT 2001 ACS
TI Internalization of *urinary**trypsin**inhibitor*in human uterine fibroblasts PY 1998

L19 ANSWER 22 OF 53 CA COPYRIGHT 2001 ACS
TI Identification and characterization of the cell-associated binding protein for *urinary**trypsin**inhibitor* PY 1998

L19 ANSWER 23 OF 53 CA COPYRIGHT 2001 ACS
TI Production of a hybrid protein consisting of the N-terminal fragment of urokinase and the C-terminal *domain* of *urinary**trypsin**inhibitor* in Escherichia coli PY 1998

L19 ANSWER 24 OF 53 CA COPYRIGHT 2001 ACS
TI The crystal structure of *Bikunin* from the inter-α- inhibitor complex: a serine protease inhibitor with two Kunitz domains PY 1998

L19 ANSWER 25 OF 53 CA COPYRIGHT 2001 ACS
TI Expression and localization of *urinary**trypsin**inhibitor* in the rat embryo PY 1997

L19 ANSWER 26 OF 53 CA COPYRIGHT 2001 ACS
TI Role of O-linked carbohydrate of human *urinary**trypsin**inhibitor* on its lysosomal membrane-stabilizing property PY 1998

L19 ANSWER 27 OF 53 CA COPYRIGHT 2001 ACS
TI Cloning of a new Kunitz-type protease inhibitor with a putative transmembrane *domain* overexpressed in pancreatic cancer PY 1998

L19 ANSWER 28 OF 53 CA COPYRIGHT 2001 ACS AN 127:246958 CA
TI Inhibition of tryptase TL2 from human T4+ lymphocytes and inhibition of HIV-1 replication in H9 cells by recombinant aprotinin and *bikunin* homologs
AU Brinkmann, Thomas; Schaefers, Jochen; Guertler, Lutz; Kido, Hiroshi; Niwa, Yasuharu; Katunuma, Nobuhiko; Tschesche, Harald
CS Institut fur Laboratoriums- und Transfusionsmedizin, Herzund Diabeteszentrum Nordrhein-Westfalen, Universitatsklinik der Ruhr-Universitat Bochum, Bad Oeynhausen, Germany
SO J. Protein Chem. (1997), 16(6), 651-660 CODEN: JPCHD2; ISSN: 0277-8033 PB Plenum DT Journal LA English
AB The serine esterase TL2 from human T4+ lymphocytes is a binding component to HIV-1 glycoprotein gp120 and seems to play a role in the HIV-1 infection mechanism. Recombinant variants of the Kunitz-type serine proteinase inhibitor aprotinin were investigated for their ability to inhibit tryptase TL2 and the binding of gp120 to this enzyme. Furthermore, the viral replication of HIV-1 was investigated in H9 cell cultures under the influence of recombinant aprotinin and *bikunin* variants. In contrast to native aprotinin, the recombinant variant [Arg15, Phe17, Glu52]aprotinin with a reactive-site sequence homologous to the V3 loop of HIV-1 gp120 showed a specific inhibition of tryptase TL2 (>80%). However, the [Leu15, Phe17, Glu52]aprotinin variant with hydrophobic subsites was the most potent inhibitor of the binding of gp120 to tryptase TL2 (68%). The authors' results show that the enzyme activity of purified tryptase TL2 is inhibited not only by variants with basic amino acids, but also those with hydrophobic residues in the reactive-site region. Therefore, tryptase TL2 is not a typical trypsin-like or chymotrypsin-like protease. Investigations on inhibition of HIV-1 replication in H9 cell cultures showed that tryptase TL2 is involved in the mechanism of virus internalization into human lymphocytes. The [Leu15, Phe17, Glu52]aprotinin showed a retardation of syncytium formation over a period of 5 days in a 1 μM concn. Similar investigations were performed with recombinant variants of *bikunin*, the light chain of human inter-α-trypsin inhibitor. Only the single-headed variant [Arg94].delta.2bikunin inhibited slightly the syncytium formation over a period of 2 days in a 2.2 μM concn. Wild-type *bikunin* and all full-length variants showed no effect, possibly due to steric hindrance by the second *domain* of the double-headed inhibitor.

L19 ANSWER 29 OF 53 CA COPYRIGHT 2001 ACS AN 127:216908 CA
TI Purification and characterization of a novel protease inhibitor specific to hepatocyte growth factor activator
AU Kawaguchi, Toshiya; Shimomura, Takeshi; Denda, Kimitoshi; Kitamura, Akiko; Kondo, Jun; Kito, Masahiro; Kagaya, Shinji; Qin, Li; Takata, Hiroyuki; Miyazawa, Keiji; Kitamura, Naomi
CS Yokohama Research Center, Mitsubishi Chemical Corporation, Yokohama, 227, Japan
SO Anim. Cell Technol.: Basic Appl. Aspects, Proc. Annu. Meet. Jpn. Assoc. Anim. Cell Technol., 8th (1997), Meeting Date 1995, 403-407. Editor(s): Funatsu, Kazumori; Shirai, Yoshihito; Matsushita, Taku. Publisher: Kluwer, Dordrecht, Neth. CODEN: 64WUA2 DT Conference LA English
AB *Hepatocyte**growth**factor**activator**inhibitor* (HAI) was purified from serum-free conditioned medium of a human stomach carcinoma cell line, and a partial amino acid sequence was detd. The sequence data revealed that HAI is a novel proteinase inhibitor which contains a Kunitz-type serine proteinase inhibitory *domain*. Purified HAI inhibited hepatocyte growth factor activator in a concn.-dependent manner, but had no significant effect on factor XIIa.

L19 ANSWER 30 OF 53 CA COPYRIGHT 2001 ACS
TI Metastasis inhibitor proteins consisting of *urinary**trypsin**inhibitor* and urokinase PY 1997 1997 1999

L19 ANSWER 31 OF 53 CA COPYRIGHT 2001 ACS AN 127:104313 CA
TI Novel protease inhibitory activities of the second *domain* of urinary trypsin inhibitory (R-020) and its effect on sepsis-induced organ injury in rat
AU Murata, A.; Toda, H.; Uda, K.-I.; Nakagawa, H.
CS Department of Surgery II, Osaka University Medical School, Suita City, 565, Japan
SO Immune Consequences Trauma, Shock Sepsis: Mech. Ther. Approaches, [Int. Congr.], 3rd (1996), Meeting Date 1994, Volume 1, 78-81. Editor(s): Faist, Eugen; Baue, Arthur E.; Schildberg, F. W. Publisher: Pabst Science Publishers, Lengerich, Germany. CODEN: 64SOAW DT Conference LA English
AB The authors used the recombinant protein R-020 coding the second *domain* of the Kunitz-type proteinase inhibitor in human *urinary**trypsin**inhibitor* to examn. its therapeutic efficacy in a rat in vivo sepsis model. R-020 could protect the host from organ injuries occurring in septic reactions, as shown by the overall improved survival rate of the rats and the strongly attenuated pathol. changes in the lungs. Thus, R-020 appears to be effective in treating sepsis-related organ dysfunction.

L19 ANSWER 32 OF 53 CA COPYRIGHT 2001 ACS
TI Recombinant preparation in Pichia of human protease inhibitor mutants with improved activity on inhibiting neutrophil elastase PY 1997

L19 ANSWER 33 OF 53 CA COPYRIGHT 2001 ACS
TI Identification and cloning of human placental *bikunin*, a novel serine protease inhibitor containing two Kunitz domains PY 1997

L19 ANSWER 34 OF 53 CA COPYRIGHT 2001 ACS
TI Characterization of placental *bikunin*, a novel human serine protease inhibitor PY 1997

L19 ANSWER 35 OF 53 CA COPYRIGHT 2001 ACS
TI *Urinary**trypsin**inhibitor*: production in the liver and reabsorption in the kidney of the rat PY 1996

L19 ANSWER 36 OF 53 CA COPYRIGHT 2001 ACS
TI Mechanism of tumor cell-induced extracellular matrix degradation. Inhibition of cell-surface proteolytic activity might have a therapeutic effect on tumor cell invasion and metastasis PY 1996

L19 ANSWER 37 OF 53 CA COPYRIGHT 2001 ACS
TI Human *urinary**trypsin**inhibitor* and fragments and their recombinant preparation with Pichia PY 1996

L19 ANSWER 38 OF 53 CA COPYRIGHT 2001 ACS
TI Sequence analysis and evolutionary aspects of piscine α-1- microglobulin/ *bikunin* mRNA transcripts PY 1995

L19 ANSWER 39 OF 53 CA COPYRIGHT 2001 ACS AN 123:221366 CA
TI Novel blood coagulation factor inhibitory activities of the second *domain* of urinary**trypsin**inhibitor* and its variants
AU Nii, Atsushi; Morishita, Hideaki; Hirose, Jiro; Yamakawa, Toru; Kanamori, Toshinori
CS Biosciences Research Laboratory, Mochida Pharmaceutical Co., Ltd., Japan
SO Nippon Kessen Shiketsu Gakkaishi (1995), 6(3), 203-7 CODEN: NKSGEL; ISSN: 0915-7441 DT Journal; General Review LA Japanese

AB A review, with 15 refs., on the title topic, discussing mol. cloning, expression, and purifn. of the second *domain* (R-020) of *urinary**trypsin**inhibitor*; inhibitory activities of R-020; and prepn. of R-020 variants.

L19 ANSWER 40 OF 53 CA COPYRIGHT 2001 ACS
TI The three heavy-chain precursors for the inter-α-inhibitor family in mouse: new members of the multicopper oxidase protein group with differential transcription in liver and brain PY 1995

L19 ANSWER 41 OF 53 CA COPYRIGHT 2001 ACS
TI Inhibition of tumor cell invasion through matrigel by a peptide derived from the *domain* II region in urinary trypsin inhibition PY 1995

L19 ANSWER 42 OF 53 CA COPYRIGHT 2001 ACS
TI Kunitz-type trypsin inhibitor prevents LPS-induced increase of cytosolic free Ca2+ in human neutrophils and HUVEC cells PY 1995

L19 ANSWER 43 OF 53 CA COPYRIGHT 2001 ACS
TI Isolation and characterization of novel blood coagulation factor Xa (FXa) inhibitor (R-020) and its variants PY 1994

L19 ANSWER 44 OF 53 CA COPYRIGHT 2001 ACS
TI Inhibitory effect of a conjugate between human urokinase and *urinary**trypsin**inhibitor* on tumor cell invasion in vitro PY 1995

L19 ANSWER 45 OF 53 CA COPYRIGHT 2001 ACS AN 122:234086 CA
TI Activities of the second *domain* of human *urinary**trypsin**inhibitor* on various enzymes
AU Nagase, Yasukazu
CS Department of Microbiology, Kyoto Prefectural University of Medicine, Kyoto, Japan
SO Kyoto-furitsu Ika Daigaku Zasshi (1994), 103(5), 623-35 CODEN: KFIZAO; ISSN: 0023-6012 DT Journal LA Japanese
AB To investigate the inhibitory spectrum of human *urinary**trypsin**inhibitor* (UTI) in more detail, cDNA coding for its 2nd *domain* was obtained and an expression plasmid pM552 was constructed. The product secreted into the cultured supernatant of transformant Escherichia coli JE5505 contg. the plasmid was then isolated. The recombinant 2nd *domain* of UTI was purified by ammonium sulfate pptn., gel filtration chromatog., ion-exchange chromatog. and reverse phase chromatog. In addn. to its already known inhibitory activities, the 2nd *domain* mol. demonstrated a concn.-dependent inhibitory effect on human blood-coagulation factor Xa and human plasma kallikrein. Moreover, it prolonged the plasma-based activated partial thromboplastin time.

L19 ANSWER 46 OF 53 CA COPYRIGHT 2001 ACS
TI Protective effect of recombinant neutrophil elastase inhibitor (R-020) on sepsis-induced organ injury in rat PY 1994

L19 ANSWER 47 OF 53 CA COPYRIGHT 2001 ACS
TI Monoclonal antibodies against trypsin-binding *domain* of human *urinary**trypsin**inhibitor* PY 1994

L19 ANSWER 48 OF 53 CA COPYRIGHT 2001 ACS AN 121:197625 CA
TI Design of variants of the second *domain* of *urinary**trypsin**inhibitor* (R-020) with increased factor Xa inhibitory activity
AU Nii, Atsushi; Morishita, Hideaki; Yamakawa, Toru; Matsusue, Tomokazu; Hirose, Jiro; Miura, Toshihisa; Isaji, Mitsuko; Horisawa, Yoshifumi; Sugihara, Keisuke; et al.
CS Bioscience Research Laboratory, Mochida Pharmaceutical Co., Ltd., Tokyo, 115, Japan
SO J. Biochem. (Tokyo) (1994), 115(6), 1107-12 CODEN: JOBIAO; ISSN: 0021-924X DT Journal LA English
AB The second *domain* (R-020) of human *urinary**trypsin**inhibitor* (UTI) exerts similar inhibitory activities on trypsin, α-chymotrypsin, leukocyte elastase, and plasmin to those of UTI itself, and addnl. inhibits coagulation factor Xa(FXa) and plasma kallikrein, on both of which UTI has no inhibitory effect. In the present study, the authors attempted to increase this FXa-inhibitory activity by modeling the structure of R-020-FXa complex and substituting one or two amino acids in R-020 using recombinant DNA technol. Mol. modeling of R-020 and FXa was performed with ref. to x-ray anal. of the complex of bovine pancreatic trypsin inhibitor (BPTI) and bovine trypsin to det. the site of amino acid modification. The expression plasmids into which R-020 genes with base substitution were inserted were prepd. and introduced into Escherichia coli to express R-020 variants. The resulting variants were purified and their enzyme inhibitory activities were measured. The FXa-inhibitory activity was increased in four variants with single amino acid substitution. With another four variants having two amino acid substitutions involving combinations of the above single amino acid substitutions, the FXa-inhibitory activity was further increased. Because the electrostatic interaction within R-020-FXa complex seemed stronger in these R-020 variants, this increase in FXa-inhibitory effect was speculated to be a consequence of more potent binding between the enzyme and the inhibitor.

L19 ANSWER 49 OF 53 CA COPYRIGHT 2001 ACS
TI TSG-6, an Arthritis-Associated Hyaluronan Binding Protein, Forms a Stable Complex with the Serum Protein Inter-α-inhibitor PY 1994

L19 ANSWER 50 OF 53 CA COPYRIGHT 2001 ACS
TI Monoclonal antibodies that recognize trypsin binding *domain* of human *urinary**trypsin**inhibitor* PY 1993

L19 ANSWER 51 OF 53 CA COPYRIGHT 2001 ACS AN 120:211333 CA
TI Novel factor Xa and plasma kallikrein inhibitory activities of the second Kunitz-type inhibitory *domain* of *urinary**trypsin**inhibitor*
AU Morishita, Hideaki; Yamakawa, Toru; Matsusue, Tomokazu; Kusuyama, Takeshi; Sameshima-Aruga, Rie; Hirose, Jiro; Nii, Atsushi; Miura, Toshihisa; Isaji, Mitsuko; et al.
CS Biosci. Res. Lab., Mochida Pharm. Co. Ltd., Tokyo, 115, Japan
SO Thromb. Res. (1994), 73(3-4), 193-204 CODEN: THBRAA; ISSN: 0049-3848 DT Journal LA English
AB *Urinary**trypsin**inhibitor* is a glycoprotein with a structure in which 2 Kunitz-type inhibitory domains are linked in a row. Two genes were isolated encoding the 70-amino-acid sequence from the 78th amino acid (Thr) to the C-terminal and the 68-amino-acid sequence from the 80th (Ala) to C-terminal of human *urinary**trypsin**inhibitor*, both which correspond to the 2nd Kunitz-type inhibitory *domain*, and then expression plasmids were constructed by ligating it to the Escherichia coli alk. phosphatase signal peptide gene. These plasmids under the control of the tryptophan promoter expressed the 2nd *domain* in E. coli strain JE5505 which lacks the membrane lipoprotein. The recombinant 2nd *domain* purified from the culture supernatant of the transformant inhibited trypsin, plasmin, leukocyte elastase, and chymotrypsin which are known to be inhibited by *urinary**trypsin**inhibitor*.In addn. it inhibited blood coagulation factor Xa and plasma kallikrein in a concn.-dependent and competitive manner, and significantly prolonged the plasma-based activated partial thromboplastin time (APTT). The truncated natural counterpart obtained by a limited degrdn. of human *urinary**trypsin**inhibitor* revealed identical inhibitory activities.

L19 ANSWER 52 OF 53 CA COPYRIGHT 2001 ACS
TI Kunitz-type proteinase inhibitors derived by limited proteolysis of the inter-α-trypsin inhibitor. V. Attachments of carbohydrates in the human *urinary**trypsin**inhibitor* isolated by affinity chromatography Y 1981

L19 ANSWER 53 OF 53 CA COPYRIGHT 2001 ACS
TI Kunitz-type proteinase inhibitors derived by limited proteolysis of the inter-α-trypsin inhibitor. IV. The amino acid sequence of the human *urinary**trypsin**inhibitor* isolated by affinity chromatography PY 1981

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Set	Items	Description
S1	23	"APROTININ --ANALOGS AND DERIVATIVES --AA"
S2	5638	"APROTININ"
S3	1029	KUNITZ
S4	156	S2 AND S3
S5	38460	GLYCOSYL?
S6	1	S4 AND S5
S7	2581	"SERINE PROTEINASE INHIBITORS"
S8	2535	DC="D27.505.373.745.800."
S9	0	S8 AND S3 AND S5
S10	94	S8 AND S3
S11	806	"RECOMBINANT PROTEINS -- PHARMACOKINETICS --PK"
[redacted]	14356	"RECOMBINANT PROTEINS -- [redacted]RMACOLOGY --PD"
S13	25964	"RECOMBINANT PROTEINS -- METABOLISM --ME"
S14	3394	"RECOMBINANT PROTEINS -- ADMINISTRATION AND DOSA"
S15	40	S8 AND S5
S16	76599	"RECOMBINANT PROTEINS"
S17	10	S15 AND S16
S18	1224	S13 AND S5
S19	1	S18 AND S3
S20	58	S11 AND S5
S21	0	S20 AND S3
S22	207	S12 AND S5 NOT (S17 OR S20)
S23	2	S3 AND S22
S24	66	S14 AND S5

1/6/1 10463203 99447443
NMR characterization of partially folded and unfolded conformational ensembles of proteins. 1999

[redacted]:0195744 20035840
[redacted]eering an unnatural Nalpha-anchored disulfide into BPTI by total chemical synthesis: structural and functional consequences. Oct 22 1999

1/6/3 10166705 99425321
Miniaturized proteins: the backbone cyclic proteinomimetic approach. Sep 17 1999

1/6/4 10120457 99083921
Selective bridging of bis-cysteinyl residues by arsonous acid derivatives as an approach to the characterization of protein tertiary structures and folding pathways by mass spectrometry.Nov 15 1998

1/6/5 10085470 97408608
Inhibition of tryptase TL2 from human T4+ lymphocytes and inhibition of HIV-1 replication in H9 cells by recombinant aprotinin and bikunin homologues. Aug 1997

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Binding of the bovine basic pancreatic trypsin inhibitor (Kunitz) to human urinary kallikrein and to porcine pancreatic beta-kallikreins A and B. Jul 5 1984

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Descriptors. *Blood Coagulation; *Factor VIIa--Antagonists and Inhibitors --Al; *Factor Xa--Antagonists and Inhibitors--Al; *Lipoproteins--Metabolism --ME; Aprotinin --Metabolism--ME; Lipoproteins--Pharmacology--PD; Recombinant Proteins--Metabolism--ME; Saccharomyces cerevisiae

CAS Registry No.: 0 (lipoprotein-associated coagulation inhibitor); 0 (recombinant Kunitz protease inhibitor); 0 (Aprotinin) Enzyme No.: EC (Recombinant Proteins); 9087-70-1 (Lipoproteins); 0 3.4.21.21 (Factor VIIa); EC 3.4.21.6 (Factor Xa)

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Thermodynamic stability effects of single peptide bond hydrolysis in protein inhibitors of serine proteinases.

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Journal of molecular biology (ENGLAND) Mar 8 1996, 256 (4) [illegible]-802, ISSN 0022-2836 Journal Code: J6V Languages: ENGLISH Document type: JOURNAL ARTICLE

Kunitz type soybean trypsin inhibitor (STI) and basic pancreatic trypsin inhibitor (BPTI) were used as model proteins to measure the thermodynamic consequences of single peptide bond hydrolysis. For each inhibitor, the reactive site cleaved form was prepared and, additionally, each inhibitor was selectively cleaved at a Met residue. Selective cleavage generally led to reducing of the T(den) value from 7 K up to 75 K. For STI cleaved at Met84 a slight stabilization (increase of T(den) by 1.0 K) was observed. In terms of deltaG(den), the difference between the most extreme cleavage effect was 11.44 kcal/mole, much larger than resulting from the theoretical effects of crosslinks. It was found that hydrolysis of a single peptide bond affects not only entropy, but also enthalpy and heat capacity parameters. Moreover, the sign of change is opposite for two inhibitors: deltaH(den) and deltaS(den) increase for both cleaved forms of STI, while they decrease for two nicked forms of BPTI. To understand the stability effects, a thermodynamic cycle analysis was applied based on comparison of stabilities of intact native and denatured states with peptide bond hydrolysis equilibria in agreement of the theoretical effect of cross-link elimination with a energy difference for the cycle revealed a good [illegible] tured protein. It appears that hydrolysis of a single peptide bond in peptide bonds in a native protein span over at least 20 orders of magnitude. They are very low for peptide bonds placed in alpha-helices and very high if cleavage reaction leads to a formation of a new secondary structure element.

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Genetically engineered serine protease inhibitor for hemostasis after cardiac operations.

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Cardiothoracic Unit, Department of Surgery, Royal Postgraduate

Annals of thoracic surgery (UNITED STATES) Apr 1996, 61 (4) pT223-30, ISSN 0003-4975 Journal Code: 683 ENGLISH Document type: JOURNAL ARTICLE Languages:

BACKGROUND: The serine protease aprotinin has been widely reported for its beneficial action in limiting blood loss after cardiopulmonary bypass (CPB). A potent human serine protease inhibitor known as protease nexin II or amyloid precursor protein has been recently isolated. A recombinant protein known as recombinant Kunitz protease inhibitor (rKPI; Scios Nova, Mountain View, CA) with sequence homology to the [illegible]-amyloid precursor protein molecule has been manufactured. METHODS: Recombinant Kunitz protease inhibitor was assessed in an ovine model of CPB as a hemostatic agent after CPB. Sheep (n = 22) underwent CPB for 90 minutes. Two thoracic drains were sited and drain losses collected for a period of 3 hours after CPB. Wounds were subjectively assessed before closure for "dryness" using a visual analogue scale. Sheep were randomized to control (n = 8), aprotinin (n = 8), and rKPI (n = 6) groups. RESULTS: Control animals had a drain loss of 409.4 +/-39.4 mL/3 h, compared with 131.3 +/- 20.3 mL/3 h for the aprotinin group and 163.7 +/- 34.3 mL/3 h for the rKPI group (p = 0.16). Hemoglobin loss was 11.6 +/- 3.6, 6.02 +/- 2.1, and 4.6 +/- 1.2 g/3 h for the control, rKPI, and aprotinin groups respectively (p = 0.25). The subjective analysis of the wounds at the end of CPB found aprotinin (1.25 +/- 0.16; p < 0.05) and rKPI (1.17 +/- 0.17; p < 0.05) animals to score significantly lower than control animals (2.63 +/- 0.42). CONCLUSIONS: On the basis of these in vivo findings, genetic modification may yield a more efficacious serine protease inhibitor with the inherent advantages of using a human-based protein.

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High-performance liquid chromatographic separation of aprotinin-like inhibitors and their determination in very small amounts.

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Department of Molecular, Cellular and Animal Biology, University of Camerino, Italy.

Journal of chromatography (NETHERLANDS) Aug 11 1993, 617 (2) p308-12, ISSN 0021-9673 Journal Code: HQF Languages: ENGLISH Document type: JOURNAL ARTICLE

A reversed-phase high-performance liquid chromatographic method for the determination and quantitative recovery of fully active aprotinin (the basic pancreatic trypsin inhibitor or Kunitz inhibitor) and aprotinin -like inhibitors in amounts down to 0.5 micrograms is reported. The method, which allows separation of aprotinin isoinhibitors characterized by small differences in the primary structure with respect to aprotinin itself, appears to be suitable for the quantitation and identification of aprotinin -like inhibitors in human biological fluids, in which they appear to be present at very low levels.

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A novel marsupial protein expressed by the mammary gland only during the early lactation and related to the Kunitz proteinase inhibitors. Jun 1 1998

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A double headed serine proteinase inhibitor--human plasma kallikrein and elastase inhibitor--from Boophilus microplus larvae. Dec 1999

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Synthesis of the [illegible] with open [illegible]

4/6/[illegible] secreted Kunitz domain 1 variants of tissue factor pathway inhibitor.

Johnson K; Zaror I; Bauer D; Choi Y; Creasey A; Innis M

Johnson K; Zaror I; Bauer D; Choi Y; Creasey A; Innis M

Chiron Technologies, Chiron Corporation, Emeryville, CA 94608, USA.

Thrombosis and haemostasis (GERMANY) Oct 1998, 80 (4) p585-7, ISSN 0340-6245 Journal Code: VQ7 Languages ENGLISH Document type: JOURNAL ARTICLE JOURNAL ANNOUNCEMENT: 9903 Subfile: INDEX MEDICUS

Tissue factor pathway inhibitors (TFPI and TFPI-2) are Kuni domain-type serine protease inhibitors which inhibit factor Vila/tissue factor (VIIa/TF) complexes in a factor Xa-dependent manner. The VIIa/TF and Xa inhibitory activity has been locali to the first two Kunitz domains, respectively. Unlike TFPI, TF has been reported to exhibit significant Xa-independent VIIa/TF inhibitory activity, perhaps due to an arginine at the P1 residu the first Kunitz domain of TFPI-2 as opposed to a lysine at comparable residue in TFPI. Two domain TFPI variants, differ the first Kunitz domain but containing the second Kunitz do of TFPI, were constructed and secreted by Saccharomyces cerevisiae in order to test the possibility that a TFPI first K domain with a P1 lysine to arginine change or a hybrid co the TFPI-2 first Kunitz domain may represent [illegible] inhibitors. When yeast supernatants were analyzed, potent activity in the Xa-dependent inhibition of VIIa/TF, r was as active as the truncated TFPI.

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Tissue factor pathway inhibitor and the current concept of blood coagulation.
Broze GJ Jr
Division of Hematology/Oncology, Jewish Hospital, Washington University Medical Center, St Louis, MO 63110, USA.
Blood coagulation & fibrinolysis (ENGLAND) Jun 1995, 6 Suppl 1 pS7-13, ISSN 0957-5235 Journal Code: A5J Contract/Grant No.: HL34462, HL, NHLBI; HL14147, HL, NHLBI Languages: ENGLISH Document type:JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
Tissue factor pathway inhibitor (TFPI) is a multivalent, Kunitz -type plasma proteinase inhibitor that regulates tissue factor-induced coagulation. TFPI directly inhibits activated factor X and, in a factor Xa-dependent manner, produces feedback inhibition of the factor VIIa/tissue factor catalytic complex. The properties of this inhibitor help explain the clinical need for 'extrinsic' and 'intrinsic' coagulation pathways and have led to a reformulation of the coagulation cascade. In the revised hypothesis, factor VIIa/tissue factor is responsible for the initiation of coagulation but, owing to TFPI-mediated feedback inhibition, amplification of the procoagulant response though the actions of factor VIII, IX and XI is required for sustained haemostasis. (40 Refs.)

10/7/63 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
08629283 96182215
Genetically engineered serine protease inhibitor for hemostasis after cardiac operations.
Ohri SK; Paratt R; Becket JM; Brannan J; Hunt BJ; Taylor KM
Cardiothoracic Unit, Department of Surgery, Royal Postgraduate Medical School, Hammersmith Hospital, London, England.
Annals of thoracic surgery (UNITED STATES) Apr 1996, 61 (4) p1223-30 ISSN 0003-4975 Journal Code: 683 Languages: ENGLISH Document type: JOURNAL ARTICLE
BACKGROUND: The serine protease inhibitor aprotinin has been widely reported for its beneficial action in limiting blood loss after cardiopulmonary bypass (CPB). A potent human serine protease inhibitor known as protease nexin II or amyloid precursor protein has been recently isolated. A recombinant protein known as recombinant Kunitz protease inhibitor (rKPI; Scios Nova Mountain View, CA) with sequence homology to the protease nexin II-amyloid precursor protein molecule has been manufactured
METHODS: Recombinant Kunitz protease inhibitor was assessed in an ovine model of CPB as a hemostatic agent after CPB. Sheep (n = 22) underwent CPB for 90 minutes. Two thoracic drains were sited and drain losses collected for a period of 3 hours after CPB. Wounds were subjectively assessed before closure for "dryness" using a visual analogue scale. Sheep were randomized to control (n = 8), aprotinin (n = 8), and rKPI (n = 6) groups.
RESULTS: Control animals had a drain loss of 409.4 +/- 39.4 mL/3 h, compared with 131.3 +/- 20.3 mL/3 h for the aprotinin group and 163.7 +/- 34.3 mL/3 h for the rKPI group (p = 0.16). Hemoglobin loss was 11.6 +/- 3.6, 6.02 +/- 2.1, and 4.6 +/- 1.2 g/3 h for the control, rKPI, and aprotinin groups respectively (p = 0.25). The subjective analysis of the wounds at the end of CPB found aprotinin (1.25 +/- 0.16; p < 0.05) and rKPI (1.17 +/- 0.17; p < 0.05) animals to score significantly lower than control animals (2.63 +/- 0.42).
CONCLUSIONS: On the basis of these in vivo findings, genetic modification may yield a more efficacious serine protease inhibitor with the inherent advantages of using a human-based protein.

10/5/57 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
08709132 96202952
Inhibitory properties of separate recombinant Kunitz -type-protease-inhibitor domains from tissue-factor-pathway inhibitor.
Petersen LC; Bjorn SE; Olsen OH; Nordfang O; Norris F; Norris K
Health Care Discovery, Vessel Wall Biology, Novo Nordisk A/S, Gentofte, Denmark.
European journal of biochemistry (GERMANY) Jan 15 1996, 235 (1-2) p310-6, ISSN 0014-2956 Journal Code: EMZ
Languages: ENGLISH Document type: JOURNAL ARTICLE
JOURNAL ANNOUNCEMENT: 9609 Subfile: INDEX MEDICUS
Tissue-factor-pathway inhibitor (TFPI) is a multivalent inhibitor with three tandemly arranged Kunitz - type-protease-inhibitor (KPI) domains. Previous studies [Girard, Y. J., Warren, L. A., Novotny , W. F., Likert, K. M., Brown, S. G., Miletich, J. R & Broze, G. J. (1989) Nature 338, 518-520] by means of site-directed mutagenesis indicated that KPI domain 1 interacts with factor VIIa, that KPI domain 2 interacts with factor Xa, and that KPI domain 3 is apparently without inhibitory function. To elucidate thereaction mechanism of this complex inhibitor, we followed a different approach and studied the inhibitory properties of fragments of TFPI obtained by expression in yeast. Results obtained with TFPI-(1-161)-peptide and separate recombinant TFPI-KPI domains 1, 2 and 3 showed that KPI domain 1 inhibited factor VIIa/tissue factor (Ki = 250 nM), KPI domain 2 inhibited factor Xa (Ki = 90 nM), and that KPI domain 3 was without detectable inhibitory function. Studies with separate KPI domains also showed that KPI domain 2 was mainly responsible for inhibition of trypsin (Ki = 0.1 nM) and chymotrypsin (Ki = 0.75 nM), whereas KPI domain 1 inhibited plasmin (Ki = 26 nM) and cathepsin G (Ki = 200 nM). The structural basis for the interaction between serine proteases and KPI domains is discussed in terms of putative three-dimensional models of the proteins derived by comparative molecular-modelling methods. Studies of factor Xa inhibition by intact TFPI (Ki approximately 0.02 nM) suggested that regions other than the contact area of the KPI domain, interacted strongly with factor Xa. Secondary-site interactions were crucial for TFPI inhibition of factor Xa but was of little or no importance for its inhibition of trypsin.
Tags: Animal, Human, In Vitro

Descriptors: Lipoproteins--Genetics--GE; *Recombinant Proteins --Pharmacology--PD; *Serine Proteinase Inhibitors--Genetics--GE; *Serine Proteinase Inhibitors--Pharmacology--PD; *Trypsin Inhibitor, Kunitz Soybean--Genetics--GE; *Trypsin nhibitor, Kunitz Soybean—Pharmacology --PD; Amino Acid Sequence; Base Sequence; Binding Sites--Genetics--GE; Cathepsins--Antagonists and Inhibitors--AI; Cell Line; Chymotrypsin --Antagonists and Inhibitors--AI; DNA Primers--Genetics--GE; Factor VIIa --Antagonists and Inhibitors--AI; Factor Xa-Antagonists and Inhibitors—AI ; Hamsters; Kinetics; Models, Molecular; Molecular Sequence Data; Molecular Structure; Pancreatic Elastase--Antagonists and Inhibitors--AI; Plasmin --Antagonists and Inhibitors--AI; Protein Conformation; Recombinant Proteins--Chemistry--CH; Recombinant Proteins--Genetics--GE; Saccharomyces cerevisiae--Genetics--GE; Serine Proteinase Inhibitors--Chemistry--CH; Trypsin Inhibitor, Kunitz Soybean--Chemistry--CH

[redacted] Registry No.: 0 (lipoprotein-associated coagulation inhibitor); [redacted]A Primers); 0 (Lipoproteins); 0 (Recombinant Proteins); 0 Serine Proteinase Inhibitors); 9088-41-9 (Trypsin Inhibitor, Kunitz Soybean) Enzyme No.: EC 3.4.- (Cathepsins); EC 3.4.21.1 Chymotrypsin); EC 3.4.21.20 (cathepsin G); EC 3.4.21.21 Factor VIIa); EC 3.4.21.36 (Pancreatic Elastase); EC 3.4.21.6 Factor Xa); EC 3.4.21.7 (Plasmin)

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xtracellular matrix-associated serine protease inhibitors (Mr 33,000, 31,000, d 27,000) are single-gene products with differential glycosylation : NA cloning of the 33-kDa inhibitor reveals its identity tissue factor pathway inhibitor-2. Nov 1 1996

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The inhibition of human factor Xa by plasminogen activator inhibitor type 1 in the presence of calcium ion, and its enhancement by heparin and vitronectin.
Urano T; Ihara H; Takada Y; Nagai N; Takada A
Department of Physiology, Hamamatsu University School of Medicine, Shizuoka, Japan.
Biochimica et biophysica acta (NETHERLANDS) Dec 5 1996, 1298 (2) p199-208, ISSN 0006-3002 Journal Code: A0W
Languages: ENGLISH Document type: JOURNAL ARTICLE
Plasminogen activator inhibitor type 1 (PAI-1), a member of serine proteinase inhibitor superfamily, is known to inhibit thrombin in the presence of either heparin or vitronectin. We analyzed possible inhibitory activity of PAI-1 on human factor Xa. PAI-1 inhibited factor Xa in the presence of calcium ion (Ca2+), whereas no inhibition was observed in the absence of Ca2+. Half maximal enhancement by Ca2+ was obtained at 0.8 mM. An equimolar complex formation between factor Xa and PAI-1 in the presence of Ca2+ was observed by SDS polyacrylamide gel electrophoresis. Both unfractionated heparin and vitronectin enhanced the inhibition only in the presence of Ca2+. Apparent second-order rate constant (ki) for the inhibition of factor Xa by PAI-1 at 5 mM Ca2+ was 1.6 x 10(4) M-1 s-1, and was enhanced 3-fold by 2 u/ml of heparin (4.6 x 10(4) M-1 s-1) and 10-fold by 100 nM vitronectin (1.6 x 10(5) M-1 s-1), respectively. The interaction between Ca(2+)-bound factor Xa and PAI-1 could be important from the view of PAI-1 neutralization and enhancement of fibrinolysis.

17/7/9 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
08864765 97072004
Extracellular matrix-associated serine protease inhibitors (Mr 33,000, 31,000, and 27,000) are single-gene products with differential glycosylation : cDNA cloning of the 33-kDa inhibitor reveals its identity to tissue factor pathway inhibitor-2.
Rao CN; Reddy P; Liu Y; O'Toole E; Reeder D; oster DC; Kisiel W; Woodley DT
Department of Dermatology, Northwestern University School of Medicine, Chicago, Illinois 60611-3008, USA.
Archives of biochemistry and biophysics (UNITED STATES) Nov 1 1996, 335 (1) p82-92, ISSN 0003-9861 Journal Code: 6SK
Contract/Grant No.: AR 41045, AR, NIAMS; AR 33625, AR, NIAMS; HL 35246, HL, NHLBI Languages: ENGLISH Document type: JOURNAL ARTICLE
Recently, we reported the identification and partial characterization of three serine protease inhibitors (M(r) 33,000, 31,000, and 27,000) from the extracellular matrix (ECM) of human umbilical vein endothelial cells and skin cells. Here, we report that a full-length cDNA clone for the 33-kDa inhibitor from SV-40 transformed human skin fibroblasts (t12FB) is identical to a recombinant trypsin/tissue factor pathway inhibitor called TFPI-2 from placenta. By immunoblotting, the three inhibitors from ECM and cell lysates demonstrated cross-reactivity with an antiTFPI-2 IgG. To further elucidate how these inhibitors are related, pulse-chase labeling of t12FB with [35S]methionine followed by immunoprecipitation with antiTFPI-2 IgG was performed on ECM and cytosolic proteins. A precursor-product relationship did not exist between the three inhibitors from ECM. In contrast, the various species of inhibitors from cytosolic fractions demonstrated a precursor-product relationship. Within the cytosolic fraction, 26-, 29-, and 30-kDa inhibitors were detected in the early chases (0 and 15 min) but they form precursors to the synthesis of the 33-kDa inhibitor which accumulated in the later chases (30 min to 1 h). When pulse-chase experiments were performed in the presence of tunicamycin, synthesis as well as sequestration of the three inhibitors into ECM was completely inhibited. In the presence of tunicamycin, the cells synthesized and sequestered a single 25.5-kDa inhibitor into ECM. Peak quantities of the 25.5-kDa inhibitor appeared in the ECM after 6 h chase while they were 1 h for the 27- and 31-kDa inhibitors and 3 h for the 33-kDa inhibitor. To further support that the three inhibitors are related but only differ in the extent of glycosylation , the 33-kDa inhibitor from the t12FB ECM was deglycosylated with N-glycosidase F and the products were identified by immunoblotting with antiTFPI-2 IgG. The enzyme released the 31-, 27-, and 25.5-kDa inhibitors from the 33-kDa inhibitor. Collectively, these results demonstrate that the ECM-associated 33-, 31-, and 27-kDa inhibitors are biosynthetic products of a single gene with differential glycosylation . The 25.5-kDa inhibitor is unglycosylated, whereas 27- and 30- to 31-kDa inhibitors are partially glycosylated and the 33-kDa inhibitor is fully glycosylated . Inhibition of glycosylation significantly retarded the rate of secretion of the inhibitor but did not prevent its association with ECM. Quantitation of the inhibitors with cell-conditioned medium and ECM fractions reveals that 70-75% were ECM-associated and 25-30% cell-associated. None or very little of the inhibitors (0-2%) remained in a conditioned medium. Because they are primarily associated with ECM, the inhibitors may play a major role in ECM remodeling and turnover.

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In vitro stability of a tissue-type plasminogen activator mutant, BM 06.022, in human plasma.
Rijken DC; Groeneveld E; Barrett-Bergshoeff MM
Gaubius Laboratory, TNO-PG, Leiden, The Netherlands.
Thrombosis and haemostasis (GERMANY) Dec 1994, 72 (6) p906-11, ISSN 0340-6245 Journal Code: VQ7 Languages: ENGLISH Document type: JOURNAL ARTICLE
BM 06.022 is a non-glycosylated mutant of human tissue-type plasminogen activator (t-PA) comprising only the kringle-2 and proteinase domains. The in vivo half-life of BM 06.022 antigen is 4- to 5-fold longer than that of t-PA antigen. The in vitro half-life of the activity of BM 06.022 at therapeutic concentrations in plasma is shorter than that of t-PA. In this study the inactivation of BM 06.022 in plasma was further investigated. Varying concentrations of BM 06.022 were incubated in plasma for 0-150 min. Activity assays on serial samples showed a dose-dependent decline of BM 06.022 activity with a half-life from 72 min at 0.3 microgram/ml to 38 min at 10 micrograms/ml. SDS-polyacrylamide gel electrophoresis (SDS-PAGE) followed by fibrin autography showed the generation of several BM 06.022-complexes. These complexes could be completely precipitated with antibodies against CI-inactivator, alpha 2-antiplasmin and alpha 1-antitrypsin. During the incubation of BM 06.022 in plasma, plasmin was generated dose-dependently as revealed by varying degrees of alpha 2-antiplasmin consumption and fibrinogen degradation. SDS-PAGE and immunoblotting showed that single-chain BM 06.022 was rapidly (i.e. within 45 min) converted into its two-chain form at concentrations of 5 micrograms/ml BM 06.022 and higher. In conclusion, BM 06.022 at therapeutic concentrations in plasma was inactivated by CI-inactivator, alpha 2-antiplasmin and alpha 1-antitrypsin.(ABSTRACT TRUNCATED AT 250 WORDS)

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Glycosylation of recombinant proteins: problems and prospects.
Jenkins N; Curling EM
Research School of Biosciences, University of Kent, Canterbury, UK.
Enzyme and microbial technology (ENGLAND) May 1994, 16 (5) 354-64, ISSN 0141-0229 Journal Code: AL3 Languages: ENGLISH Document type: JOURNAL ARTICLE; REVIEW; REVIEW, ACADEMIC (165 Refs.)

20/7/55 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
08228954 89114703
The influence of carbohydrate structure on the clearance of recombinant tissue-type plasminogen activator.
Rijken DC; Refino CJ; Leonard CK; O'Connor JV; Crowley C; McCabe J; Tate K; Nakamura G; Powers D; Levinson A; et al
Department of Pharmacological Sciences, Genentech, Inc., South San Francisco, CA.
Thrombosis and haemostasis (GERMANY, WEST) Oct 31 1988, 60 (2) p255-61 , ISSN 0340-6245 Journal Code: VQ7 Languages: ENGLISH Document type: JOURNAL ARTICLE

Modification of the carbohydrate structures of recombinant tissue-type plasminogen activator (rt-PA) can increase or decrease its rate of clearance in rabbits. When rt-PA was treated with sodium periodate to oxidize carbohydrate residues, the rate of clearance was decreased from 9.6 +/- 1.9 ml min-1 kg-1 to 3.5 +/- 0.6 ml min-1 kg-1 (mean +/- SD, n = 5). A similar change in the clearance of rt-PA was introduced by the use of endo-beta-N-acetyl-glucosaminidase H (Endo-H), which selectively removes high mannose asparagine-linked oligosaccharides; the clearance of Endo-H-treated rt-PA was 5.0 +/- 0.5 ml min-1 kg-1. A mutant of rt-PA was produced with an amino acid substitution at position 117 (Asn replaced with Gln) to remove a potential glycosylation site that normally contains a high mannose structure. The clearance of this material was also decreased, similar to the periodate and Endo-H-treated rt-PA. Conversely, when rt-PA was produced in the CHO 15B cell line, which can produce only high mannose oligosaccharide structures on glycoproteins, the clearance was increased by a factor of 1.8. These results demonstrate that the removal of rt-PA from the blood depends significantly upon the nature of its oligosaccharide structures.

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Glycosylation and biological activity of CAMPATH-1H expressed in different cell lines and grown under different culture conditions.
Lifely MR; Hale C; Boyce S; Keen MJ; Phillips J
Department of Cell Biology, Wellcome Research Laboratories, Beckenham, Cambridge, UK.
Glycobiology (ENGLAND) Dec 1995, 5 (8) p813-22, ISSN 0959-6658 Journal Code: BEL Languages: ENGLISH Document type: JOURNAL ARTICLE
CAMPATH-1H (where CAMPATH is a trade mark of Wellcome group companies), a humanized IgG antibody used in the therapy of lymphoma, leukaemia and rheumatoid arthritis, has been expressed in Chinese hamster ovary, Y0 myeloma and NS0 myeloma cell lines. These engineered cell lines were grown under different culture conditions, and the antibody isolated and purified. N-Linked oligosaccharides, on the CH2 heavy chain region of the antibody, were isolated and analysed by hydrazinolysis, high-performance anion-exchange chromatography with pulsed amperometric detection, laser-desorption mass spectrometry and sequential exoglycosidase treatment. Both the glycosylation pattern and the biological activity of CAMPATH-1H, as measured by antibody-dependent cell-mediated cytotoxicity, were markedly affected by the cell line used to express the antibody. It is concluded that glycosylation of the antibody may be important in the clinical outcome of therapy.

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Reversible regulation of tissue factor-induced coagulation by glycosyl phosphatidylinositol-anchored tissue factor pathway inhibitor. Mar 2000

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07694846 94086500
Kinetics of factor Xa inhibition by tissue factor pathway inhibitor.
Huang ZF; Wun TC; Broze GJ Jr
Division of Hematology/Oncology, Jewish Hospital, Washington University Medical Center, St. Louis, Missouri 63110.
Journal of biological chemistry (UNITED STATES) Dec 25 1993, 268 (36) p26950-5, ISSN 0021-9258 Journal Code: HIV Contract/Grant No.: HL-34462, HL, NHLBI Languages: ENGLISH Document type: JOURNAL ARTICLE
Tissue factor pathway inhibitor is a multivalent, Kunitz -type proteinase inhibitor. It directly inhibits factor Xa and, in a factor Xa-dependent fashion, produces feedback inhibition of the factor VIIa/tissue factor catalytic complex which is responsible for the initiation of coagulation. Human recombinant TFPI (rTFPI) produced in Escherichia coli was used to define the kinetic constants describing the human factor Xa:TFPI interaction. The inactivation of factor Xa by E. coli-rTFPI is indistinguishable from that of rTFPI produced in mammalian SK-hepatoma cells, suggesting that post-translational modifications such as glycosylation and phosphorylation do not play a major role in the inhibitory process. The slow, tight-binding inhibition of factor Xa follows the scheme: [formula: see text] Where the enzyme (E) and inhibitor (I) form an initial, immediate collision complex (EI) that then isomerizes slowly to a tightened final EI* complex. In the absence of other additions, the initial Ki (=k2/k1) and final Ki* for the inhibition of factor Xa by E. coli-rTFPI are 1.24 nM and 26.4 pM, respectively. In the presence of calcium ions (5 mM) the interaction between factor Xa and rTFPI is substantially weaker, with a Ki of 42.7 nM and Ki* of 85.2 pM. The addition of other components of the prothrombinase complex produces enhanced factor Xa inhibition predominantly through an effect on the initial Ki. In the presence of calcium ions and saturating concentrations of phospholipids and factor Va, the Ki and Ki* for factor Xa inactivation are 2.04 nM and 52.3 pM. The enhancing effect of heparin on the inhibitory process is concentration dependent and exhibits an optimum, reminiscent of the "template" model for heparin's acceleration of thrombin and factor Ixa inhibition by antithrombin III. At optimal concentrations, the major mechanism of heparin action is also a reduction in the Ki of the initial encounter complex between factor Xa and rTFPI.

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Development of antibodies to unprotected glycosylation sites on recombinant human GM-CSF [see comments]
Gribben JG; Devereux S; Thomas NS; Keim M; Jones HM; Oldstone AH; Linch DC
Department of Haematology, Faculty of Clinical Sciences, University College and Middlesex School of Medicine, London, UK.

Lancet (ENGLAND) Feb 24 1990, 335 (8687) p434-7, ISSN 0140-6736 Journal Code: L0S Comment in Lancet 1990 May 19;335(8699):1217
Languages: ENGLISH Document type: CLINICAL TRIAL; CONTROLLED CLINICAL TRIAL; JOURNAL ARTICLE
In 4 out of 16 patients receiving recombinant human granulocyte macrophage colony stimulating factor (rhGM-CSF) in phase I/II studies antibodies developed to the recombinant protein. The antibodies react with sites on the native protein backbone which are normally protected by O-linked glycosylation but which are exposed in rhGM-CSF produced in yeast and Escherichia coli. Antigenicity of recombinant human proteins due to non glycosylation may have relevance to the choice of host system for production of factors for clinical use.

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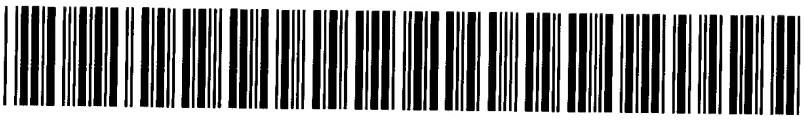

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